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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,884	03/12/2004	Viswanathan Srinivasan	P24615	4898

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EXAMINER	
SASAN, ARADHANA	
ART UNIT	PAPER NUMBER
1609	

NOTIFICATION DATE	DELIVERY MODE
05/25/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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TH

Office Action Summary	Application No.	Applicant(s)	
	10/798,884	SRINIVASAN ET AL.	
	Examiner	Art Unit	
	Aradhana Sasan	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-98* is/are pending in the application.

4a) Of the above claim(s) *22,53-71 and 88-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23-52,72-87 and 92-98* is/are rejected.

7)☒ Claim(s) *78* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :10/27/06, 2/7/06, 5/16/05, 8/17/04.

DETAILED ACTION

1. Receipt is acknowledged of applicant's response to Restriction Requirement filed on May 4, 2007.

Status of Application

Election/Restrictions

2. Applicant's election with traverse of Group I (claims 1-52, 72-77, and 78-98 in the reply filed on May 4, 2007 is acknowledged. The traversal is on the ground(s) that there is no serious burden even if the inventions of Groups I to IV are distinct and that the searches for inventions I to IV should significantly overlap. This is not found persuasive because the search for solid dosage forms (tablets) and the search for liquid dosage forms (suspensions or gels) will be different. The process of making a solid dosage form and a liquid dosage form would also require a different search. The inventions as claimed do not encompass overlapping subject matter.

3. Upon further review of the claims, it appears that claims 22, 88-91 are drawn to a liquid dosage form but are dependent on claim 78 (which is drawn to a dosage form with different layers and therefore, to a solid dosage form or a tablet). Claims 88-91 should have been part of Group II (drawn to a liquid dosage form) in the original restriction requirement. Since applicant elected Group I, claims 88-91 will be withdrawn from consideration.

The restriction requirement is still deemed proper and is therefore made FINAL.

4. Claims 53-71, 22, and 88-91 are withdrawn from consideration.

5. Claims 1-52, 72-87, 92-98 are being presented for examination.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on 10/27/06, 2/7/06, 7/7/05, 5/16/05, and 8/17/04 were filed. The submissions are in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the examiner is considering the information disclosure statements.

See attached copy of PTO-1449.

Oath/Declaration

7. Page 4 of the Oath/Declaration (including the information for inventors Ralph Brown, David Brown, Himanshu Patel, Juan Carlos Menendez, and Venkatesh Balasubramanian) is not legible. Submission of a legible copy is required.

Specification

8. The use of the following trademarks has been noted in this application: EUDRAGIT (Pages 20, 21, 24-29, 38-41, 51-57), METHOCEL (Pages 20, 21, 24-29, 36-42, 50, 51), POVIDONE (Pages 22, 23, 32-35, 45-47, 50, 51), KOLLIDON (Pages 30, 31, 36, 37, 43, 44, 52, 53-57), CARBOPOL (Pages 53, 57), AQUACOAT (Pages 52-57), AMBERLITE (Pages 52-53), POLYSORBATE (Pages 53, 57). They should be written in all capital letters wherever they appear; or alternatively, they should be denoted with the registered trademark symbol, ®, and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

9. Claim 78 is objected to because of the following informalities: The phrase "wherein the dosage form releases the at least one first morphine derivative at least one of over a different period" should be "wherein the dosage form releases the at least one first morphine derivative over a different period". Appropriate correction is required.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-3, 18-21, 78-80, 92-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara et al. (US 6,699,502).

The claimed invention is a pharmaceutical dosage form that contains a morphine derivative with antitussive activity in combination with at least one additional active ingredient. The dosage form releases the morphine derivative and the additional active ingredient at rates that provide pharmaceutically suitable plasma concentrations over similar periods of time. The dosage form comprises tablets, bi-layered tablets, and multi-layered tablets.

Fanara teaches a pharmaceutical composition (including a multi-layered pharmaceutical composition) for oral administration that allows the release of at least one active substance and includes a matrix (Abstract). Fanara teaches, "the release of

active substances during oral administration can be controlled by means of matrix-type pharmaceutical compositions" (Col. 1, lines 14-16). The compositions "can be administered in a few daily doses, ideally in a single daily dose" (Col. 1, lines 9-13). Fanara further teaches, "it is increasingly advantageous to be able to simultaneously administer by oral route an active substance released immediately after administration, and the same or a second active substance released gradually and regularly after administration ... this makes it possible to obtain combined therapeutic effects by means of two active substances having very different pharmacokinetic profiles" (Col. 2, lines 36-50). This reference also teaches that "controlled-release pharmaceutical compositions can be used in combination with an immediate-release pharmaceutical composition for the same or for another active substance, in a single unit intended to be administered orally" (Col. 3, lines 32-37). Antihistamines, antitussives, such as codeine, morphine, and their pharmaceutically acceptable salts, along with pseudoephedrine, and phenylepherine may be included in the composition (Col. 4, lines 54-67). The pharmaceutical composition can be in the form of tablets (Col. 5, lines 18-20). The tablets can be bilayered (Col. 5, lines 48-58) or multilayered (Col. 6, lines 20-26). Example 7 of this reference discloses a double-layer tablet (with the two layers stuck to each other) containing 15mg doses of hydrocodone bitartrate (10mg of the hydrocodone is in a controlled release layer and 5mg of the hydrocodone is in an immediate release layer (Col. 12, line 25-64).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition having combined

therapeutic effects of more than one active substance, as suggested by Fanara, and produce the instant invention.

The pharmaceutical dosage form comprising a first drug (morphine derivative having antitussive activity) and a second drug where the dosage form provides a plasma concentration within a therapeutic range of the second drug over a period which is coextensive with at least about 70% of a period over which the dosage form provides a plasma concentration within a therapeutic range of the first drug would have been obvious to one skilled in the art over Fanara. As mentioned above, Fanara teaches simultaneously administering more than one active substance and combining the therapeutic effects of active substances with different pharmacokinetic profiles (Col. 2, lines 36-50) and includes antitussives, antihistamines, codeine, and morphine as possible active substances in the composition. In order to have the combine therapeutic effects of active substances, it would have been obvious to one with ordinary skill in the art that the period of therapeutic effectiveness of the first active substance would be coextensive with the period of therapeutic effectiveness of the second active substance, especially if the two active substances are related to similar (antitussive) therapeutic activities.

Regarding instant claims 18-21, the tablet (bilayered) and comprising a matrix with the first drug and particles with the second drug would have been obvious to a person with ordinary skill in the art over the Fanara teaching of bilayered tablets and matrix.

One of ordinary skill in the art would have been motivated to do this because the pharmaceutical composition as taught by Fanara allows the release of the "active substances such that a satisfactory therapeutic effect is observed over fairly long periods, for example in only one or even two daily doses" (Col. 3, lines 22-27).

12. Claims 4-7, 15-17, 23-29, 30-36, 38-44, 47, 49-52, 72-77, 81-87, and 97-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara et al. (US 6,699,502) as applied to claims 1-3, 18-21, 78-80, 92-96, above, in view of Jaeger (US 3,914,425).

The teaching of Fanara is stated above.

Fanara does not expressly teach codeine phosphate as the active substance.

Jaeger teaches an antitussive codeine composition. Example 2 of this reference illustrates a three-layer "pill" or tablet containing codeine phosphate (Col. 2, lines 43-47). "An intermediate layer containing 6mg each of the two active ingredients was protected by a thin coating ... and the outer layer contained 18mg codeine phosphate". Jaeger also teaches "preparations containing codeine may additionally contain antihistamines such as triprolidine hydrochloride, decongestants such as pseudoephedrine hydrochloride, and expectorants such as glyceryl guaiacolate" (Col. 3, lines 3-7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition having combined therapeutic effects of more than one active substance, as suggested by Fanara, in view

of the codeine phosphate and second active substances (antihistamines, decongestants, and expectorants) as suggested by Jaeger and produce the instant invention.

Regarding instant claims 51-52, one with ordinary skill in the art would use the teachings of Fanara and Jaeger to produce tablets with multiple layers, where the multiple layers were adjacent to each other, or one layer surrounding the other.

Regarding instant claims 12-14, 47, and 73 one with ordinary skill in the art would use the teachings of Fanara and Jaeger to make a pharmaceutical composition by using drug combinations (antitussives, antihistamines, decongestants, expectorants) with drugs having different plasma half-lives in order to optimize the release of drugs over time. Drugs that are part of the immediate release would have a different plasma half-life than drugs that are part of the controlled release in order to maintain drug release for optimal therapeutic effect.

Regarding instant claims 15-17, 28-29, and 72-74, one with ordinary skill in the art would use the teachings of Fanara and Jaeger to make pharmaceutical compositions using drugs with different pharmacokinetic profiles (Fanara, Col. 2, lines 46-50). The claim limitations of periods of plasma concentration within the therapeutic range of the second drug being coextensive with at least about 80%, 90% or 95% of periods of plasma concentration within the therapeutic range of the first drug would have been obvious over the different pharmacokinetic profiles taught by Fanara in view of the antitussive codeine composition taught by Jaeger.

Regarding instant claims 97-98, a person with ordinary skill in the art would use the teachings of Fanara and Jaeger to make a pharmaceutical dosage form with a morphine derivative as the first drug and the second drug. Furthermore, Fanara also teaches, "as regards the dose of active substance used, it depends on the effective dose and may therefore vary within very wide limits depending on the said active substance" (Col. 5, lines 1-3). A person with ordinary skill in the art would formulate the composition in order to optimize the plasma concentration of the morphine derivative so that release of the morphine derivative from the two layers does not exceed the safe limit (maximum plasma concentration of the therapeutic range) of the morphine derivative.

One of ordinary skill in the art would have been motivated to do this because the pharmaceutical composition as taught by Fanara allows the release of the "active substances such that a satisfactory therapeutic effect is observed over fairly long periods, for example in only one or even two daily doses" (Col. 3, lines 22-27). The second drugs taught by Jaeger would have been obvious to one skilled in the art as supplementing the antitussive first drugs for ameliorating cough symptoms.

13. Claims 8-11, 37, 45-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fanara et al. (US 6,699,502) as applied to claims 4-7, 15-17, 23-29, 30-36, 38-44, 47, 49-52, 72-77, 81-87, and 97-98, above, in view of Jaeger (US 3,914,425) and further in view of Findlay et al. (US 4,650,807).

The teachings of Fanara and Jaeger are stated above.

Fanara and Jaeger do not expressly teach chlorpheniramine, promethazine, and guaifenesin.

Findlay teaches antihistaminic compositions. These compositions include tablets (Col. 5, lines 33-35). Antihistamines such as pheniramines, and promethazine are disclosed (Col. 1, lines 26-28). It is also taught that, "the active compound may be formulated with a sympathomimetic agent such as decongestants pseudoephedrine or phenylpropanolamine, an antitussive such as codeine ... or an expectorant such as guaifenesin" (Col. 5, lines 9-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the pharmaceutical composition with combined therapeutic effects of more than one active substance, as suggested by Fanara, in view of the codeine phosphate and second active substances (antihistamines, decongestants, and expectorants) as suggested by Jaeger and further in view of the specific antihistamines and expectorant as suggested by Findlay and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because the specific active substances taught by Findlay supplement the antitussive first drugs for ameliorating cough symptoms.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-52, 72-77 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 4-13, 15-21, 25-35, 38-40, 43-50, 68, 70, 73-77 of copending Application No. 10/736,902 ('902 hereinafter). Although the conflicting claims are not identical, they are not patentably distinct from each other because the first drug of the instant application is a morphine derivative, whereas the first drug of '902 is promethazine and a pharmaceutically acceptable salt thereof. One with ordinary skill in the art would use various drugs that were compatible in the composition. Promethazine is an antihistamine and since an antihistamine can be a component of the instant dosage form (second drug of instant claim 5), one with ordinary skill in the art would be motivated to use it in the composition.

16. Claims 1-52, 72-73, 75-78, 83, 85-87, 92-98 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-22, 24-25, 27-36, 39-40, 44-50, 69-70, 73-76, 79, 83-85, 94-99 of copending Application No. 10/910,806 ('806 hereinafter). Although the conflicting claims are not

identical, they are not patentably distinct from each other because the first drug of the instant application is a morphine derivative, whereas the first drug of '806 is carbetapentane and a pharmaceutically acceptable salt thereof. One with ordinary skill in the art would use various drugs that were compatible in the composition. Carbetapentane is a cough suppressant and since an expectorant or a decongestant can be a component of the instant dosage form (second drug of instant claim 5), one with ordinary skill in the art would be motivated to use a cough suppressant in the composition.

17. Claims 1-52, 72-88 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-87 of copending Application No. 10/939,351 ('351 hereinafter). Although the conflicting claims are not identical, they are not patentably distinct from each other because the first drug of the instant application is a morphine derivative, whereas the first drug of '351 is phenylepherine and a pharmaceutically acceptable salt thereof. One with ordinary skill in the art would use various drugs that were compatible in the composition. Phenylepherine is a decongestant and since a decongestant can be a component of the instant dosage form (second drug of instant claim 5), one with ordinary skill in the art would be motivated to use it in the composition.

18. Claims 1-52, 72-98 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7, 10-20, 25, 27-50, 68-76, and 80-84 of copending Application No. 11/012,267 ('267 hereinafter). Although the conflicting claims are not identical, they are not patentably distinct from

each other because the first drug of the instant application is a morphine derivative, whereas the first drug of '267 is diphenhydramine and a pharmaceutically acceptable salt thereof. One with ordinary skill in the art would use various drugs that were compatible in the composition. Diphenhydramine is an antihistamine and since an antihistamine can be a component of the instant dosage form (second drug of instant claim 5), one with ordinary skill in the art would be motivated to use it in the composition.

19. Claims 1-8, 23, 75-77 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-10, 25-26, 28-30, 32 of copending Application No. 11/115,293 ('293 hereinafter). Although the conflicting claims are not identical, they are not patentably distinct from each other because the first drug of the instant application is a morphine derivative, whereas the first drug of '293 is promethazine and a pharmaceutically acceptable salt thereof. One with ordinary skill in the art would use various drugs that were compatible in the composition. Promethazine is an antihistamine and since an antihistamine can be a component of the instant dosage form (second drug of instant claim 5), one with ordinary skill in the art would be motivated to use it in the composition.

20. Claims 1, 5-7, 9-18, 21-23, 28-29, 30-33, 39-42, 50-51, 72-77, and 78-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6-8, 12-13, 17-20, 21-24, 28-34, 38-41, 47-50, 60-65, 67-70, 73-74, 79-83, 86-90, 92, 95-96, 114, 117-119 of copending Application No. 11/115,321 ('321 hereinafter). Although the conflicting claims are not identical, they

are not patentably distinct from each other because the first drug of the instant application is a morphine derivative, whereas the first drug of '321 is an antitussive that comprises a morphine derivative. Since a morphine derivative having antitussive activity is a component of the instant dosage form (first drug of instant claim 1), one with ordinary skill in the art would be motivated to use it in the composition.

21. These are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Conclusion

1. No claims are allowed.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).